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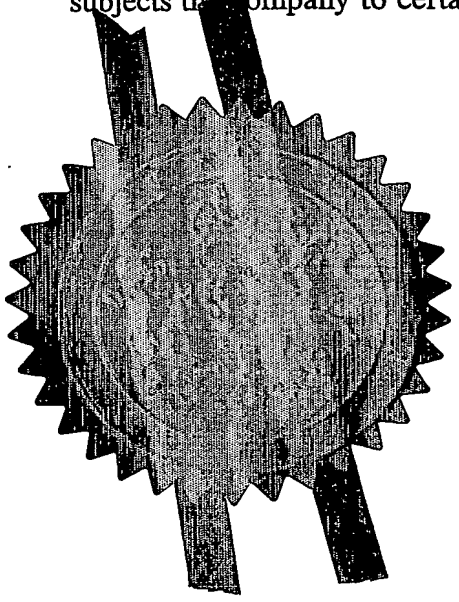

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Request for grant of a patent

16 AUG 2002

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16AUG02 E741507-2 002481
P01/7700 0.00-0219068.4

2. Patent Application Number
(the Patent Office will fill in this part) — 0219068.4

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

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Patents ADP number *(if you know it)* 7836703001

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — "Apparatus and Method"

5. Name of your agent *(if you have one)* — Murgitroyd & Company

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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Any other document (please specify)	-

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Signature MURGITROYD & COMPANY Date 13/08/02

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Apparatus and Method

This invention relates to a method and apparatus for measuring intracompartmental pH, and especially but not exclusively to measuring intracompartmental pH for the diagnosis of Acute Compartment Syndrome.

Acute compartment syndrome (ACS) is a surgical emergency which if not recognised early may lead to crippling deformities, loss of limb or even death.

Compartment syndrome has been defined as "a condition in which increased pressure within a limited space compromises the circulation and function of tissues in that space"[1]. It is most commonly seen following injuries of the leg but may also occur in the upper limb, and following ischaemic re-perfusion injuries and burns. Furthermore, sub-clinical compartment syndromes have occurred following reaming of the medullary canal in the nailing of long bone fractures[2].

Early diagnosis and prompt surgical intervention is essential to avoid the complications which may ensue. These include neurological deficit, muscle necrosis, acute renal failure, amputation and loss of life. Currently, the diagnosis of acute compartment syndrome is based on clinical assessment and intra-compartmental (IC) pressure monitoring. Extreme pain exacerbated by passive stretching of the muscles in the compartment and paraesthesia, are the most reliable signs, but may only become apparent in the later stages of acute compartment syndrome, and are not reliable in the unconscious, neurologically impaired or paediatric patient. In these circumstances invasive methods of monitoring IC pressure are therefore deemed essential[3].

Compartment pressure monitoring has been advocated since 1975[4] but debate continues over the clinical indications for its use. There are a number of pressure monitors available but most rely on a column of fluid leading to inaccuracies.

According to the present invention, there is provided a method of measuring intracompartmental pH, including the step of inserting a pH sensor directly into a muscle.

Typically, the method is used in the diagnosis of Acute Compartment Syndrome. Typically, the acute compartment syndrome is caused by a fractured limb.

The pH of muscle is a good indicator of its metabolic state with a normal physiological range of 6.95 to 7.2[5]. As the pressure in the compartment increases, blood flow ceases and lactic acid builds up, reducing the pH. By using a method of observing the changing pH of skeletal muscle tissue, it is possible to identify muscle which is at risk of irreversible damage prior to the development of clinical signs.

A second probe may also be provided to measure the intracompartmental pressure; the pH and pressure measurements can be used in conjunction to provide a diagnosis.

Preferably, the or each sensor is mounted on a respective catheter. Preferably, the or each catheter is inserted into the muscle through a respective cannula.

Preferably, the or each cannula is inserted into skeletal muscle in an orientation that is generally parallel to the muscle fibres. Preferably, the or each cannula is inserted into the muscle adjacent to, but not communicating with, the fracture site.

Preferably, the or each sensor is monitored continuously for at least 24 hours.

Preferably, the reading from the or each sensor is compared with a calibrated scale to determine the extent of muscle damage. Typically, the reading

from the or each sensor is used to determine if a fasciotomy should be performed.

According to a second aspect of the present invention, there is provided apparatus for measuring intracompartmental pH, the apparatus including a pH sensor.

Preferably, the apparatus is suitable for use in diagnosing soft tissue conditions, such as ischaemia. Preferably, the apparatus is suitable for use in the diagnosis of Acute Compartment Syndrome.

Preferably, the pH sensor is mounted on a catheter. Typically, the catheter is glass-tipped. Preferably, the glass is durable, heat-strengthened and fracture-proof.

Alternatively, the catheter is antimony-tipped.

An antimony-tipped catheter allows both the pH sensor and the pressure sensor to be mounted on the same catheter.

Preferably, the apparatus also includes a pressure sensor. Preferably, the pH sensor is connected to a pH recorder. Preferably, the pressure sensor is connected to a pressure monitoring system.

Typically, the pressure sensor is mounted on a second catheter. Alternatively, both the pH sensor

and the pressure sensor are mounted on the same catheter. In this case, the pressure sensor and the pH sensor are preferably connected to the same monitoring system, which monitors and records both pressure and pH.

Optionally, two or more pH sensors are provided. Optionally, two or more pressure sensors are provided.

According to a third aspect of the present invention, there is provided the use of a pH-monitoring device for the diagnosis of Acute Compartment Syndrome.

According to a fourth aspect of the present invention, there is provided a pH-monitoring device adapted to diagnose Acute Compartment Syndrome.

The invention also provides a method of determining information concerning the condition of soft tissue, the method comprising the steps of inserting a pH sensor into the soft tissue and measuring the intracompartmental pH in the tissue.

The invention also provides a method of diagnosing ischaemia in a tissue, the method comprising the steps of inserting a pH sensor into the tissue, and measuring the intracompartmental pH in the tissue.

The tissue is typically muscle.

An embodiment of the invention will now be described by way of example only and with reference to the following drawings, in which:-

Fig 1 shows a side view of a catheter with a pH monitor mounted thereon;

Fig 2 shows a partial cross-section of a fractured limb, into which catheters with sensors are inserted;

Fig 3a shows a graph of pH as a function of time for example 1 during tourniquet inflation;

Fig 3b shows a graph of the mean pH changes from the Fig 3a graph;

Fig 4a shows a graph of pH as a function of time for example 1 following release of tourniquet;

Fig 4b shows a graph of the mean pH changes from the Fig 4a graph;

Fig 5 shows a graph of pH and pressure as functions of time for a patient with Acute Compartment Syndrome;

Fig 6 shows a graph of pH and pressure as functions of time for a patient who did not have Acute Compartment Syndrome;

Fig 7 shows a graph of pH and delta pressure (diastolic blood pressure minus IC pressure) as functions of time for the patient of Fig 5; and

Fig 8 shows a graph of pH and delta pressure (diastolic blood pressure minus IC pressure) as functions of time for the patient of Fig 6.

Fig 1 shows a sterile 1.5mm glass-tipped catheter 1 (made of durable, heat-strengthened, fracture-proof glass). A pH sensor probe 5 is mounted on the tip of the catheter 1.

Fig 2 shows a portion of a lower leg of a patient into which is inserted the catheter 1 of Fig 1. The catheter is inserted into skeletal muscle in the proximity of a fracture in the patient's tibia. The catheter 1 is connected to a pH recorder 10 via a sterilised adapter cable 15. A suitable pH recorder is the Flexilog 2010 dual-channel pH recorder (Oakfield instruments), which permits continuous monitoring of intracompartmental (IC) pH, accurate to two decimal places.

Fig 2 also shows a second catheter 2 connected to a pressure monitoring system 11, which is used to continuously monitor IC pressure. A suitable system is the Kodiag mobile pressure monitoring system (B Braun), which allows more accurate monitoring of pressure compared with other available devices[5], and is also easy to use and sterilise. (It is not

necessary to use these specific pressure and pH monitors; other similar devices could be used).

The catheters 1, 2 are inserted, typically through 14 gauge Adsyte cannulas placed generally parallel to the muscle fibres, and adjacent to each other, into the muscle compartment adjacent to, but not communicating with, the fracture site. For example, if the apparatus is being used to diagnose suspected acute compartment syndrome caused by a tibial shaft fracture, the probes are inserted into the anterior compartment of the lower leg. For a femoral shaft fracture, the probes are inserted into the lateral portion of the anterior compartment of the thigh. The pH and pressure monitors are placed in the muscle through anaesthetised, surgically sterile skin.

The patient's blood pressure is recorded at 60-minute intervals (Critikon, Pro 300, GE Medical) to allow the delta pressure to be calculated (diastolic blood pressure minus IC pressure). A sustained delta pressure value of 30mmHg or less is currently the most frequently used indicator for surgical intervention[4].

Intracompartmental pressure and pH are recorded continuously for at least 24 hours post-injury or for longer as clinically indicated.

In order to correlate the damage sustained by skeletal muscle with specific levels of IC pressure

and pH, data was collected from patients. Patients underwent surgical fixation of their fracture under general anaesthesia, without the clinical need for fasciotomies, undergo two needle muscle biopsies (Allegiance, 14G disposable needle). Open muscle biopsies are performed on patients having fasciotomies as part of their procedure. The samples are taken at specific pH levels across the whole available range, and a number of tests are run on each biopsy to assess the presence and extent of reversible and irreversible muscle damage.

The muscle biopsy is wrapped immediately in a damp saline gauze swab and placed within a sealed, airtight sterile container awaiting transfer to the laboratory. Due to the stability of the proteins and substrates to be studied, muscle biopsies can be stored at 4°C awaiting collection. On arriving at the laboratory, the muscle biopsies are carefully oriented in relation to the direction of the fibres and then SNAP frozen. The following investigations are then undertaken on frozen cross-sections:

Glycogen: to assess myocyte energy reserves using the Periodic Acid Schiff (PAS) and PAS-digested methods.

Acid phosphatase activity: to assess tissue degeneration and the presence of necrotic muscle.

Histochemistry: to detect the presence of myosin-ATPase (used for muscle fibre typing), NADH and succinate dehydrogenase (as markers of mitochondrial activity).

Immunohistochemistry: to assess cell membrane integrity using β-spectran.

Biochemistry: The muscle biopsies for biochemical analysis are SNAP frozen immediately after being obtained, and stored thereafter at -80•C awaiting analysis. Specimens are then freeze dried using equipment available in the laboratory, and thereafter pulverised using a pestle and mortar. The powder is reconstituted using appropriate buffered solutions, and homogenised prior to centrifugation. The supernatant is added to the appropriate enzyme/ reagent mixture and incubated for 30 minutes at 25°C prior to fluorimetric assay at 340 and 460nm. The tissue concentrations of the following compounds are then ascertained:

Lactate: to assess the degree of muscle glycolysis

Creatine / Creatine Phosphate: used as a ratio to determine levels of muscle ischaemia.

For the two tests with binary outcomes (β-spectran & acid phosphatase) providing evidence of irreversible muscle damage, the results are compared using t-tests. Appropriate transformations are used if the data for pH and pressure are not normally distributed. The results of the remaining laboratory analyses are plotted against pH and pressure and are supported with Pearson or Spearman's correlations depending on the distribution of the data. Modifications to these methods and reagents may be incorporated.

Thus, pH and pressure readings taken from a patient's muscle can be compared to the correlated results, and used to judge the extent of muscle damage and a decision can be made as to whether a fasciotomy should be performed.

Example 1

The aims of this example were to ascertain the suitability, ease of use and accuracy of the pH recorder in human skeletal muscle. pH was measured continuously in the anterior compartment of the lower leg during surgery in 24 patients undergoing elective knee arthroscopy and 8 patients having a total knee replacement, under either general or spinal anaesthesia. In all patients a tourniquet was placed around the appropriate thigh and inflated to 250 or 300mmHg of pressure prior to the procedure. The pH probe was inserted into the mid-portion of tibialis anterior approximately 5cm below and 1-2cm lateral to the tibial tubercle following sterile preparation of the limb and before the tourniquet was inflated. It remained in situ for 15 and 30 minutes post tourniquet release for the arthroscopy and the total knee replacement patients respectively. Blood pressure and peripheral oxygen saturation were recorded at 5 minute intervals and an initial end tidal carbon dioxide level was noted prior to tourniquet inflation if the patient was having a general anaesthetic.

Arthroscopy study group

This example covered eighteen men and seven women (mean age of 41 years, mean tourniquet time of 21 minutes). The mean muscle pH before the tourniquet was inflated was 6.9. This decreased by 0.3 to 6.6 prior to the tourniquet being released. Fifteen minutes after the tourniquet was deflated the muscle had recovered by an average of 0.16 of a pH unit to 6.76.

Total knee replacement study group (see figs 3 and 4).

This group of patients included 3 males and 5 females (mean age of 68 years, mean tourniquet time of 79 minutes). The mean pH prior to tourniquet inflation was slightly lower than the arthroscopy group at 6.7, and decreased to 6.2 before the tourniquet was released. Fifteen minutes later, muscle pH had recovered by 0.28 of a pH unit to 6.48, with further recovery of 0.16 to 6.64 by 30 minutes (total recovery of 0.44).

The pH system was easy to use and the pH decreased during the time of tourniquet inflation and recovered on release. The average pH recorded prior to release of the tourniquet in the knee replacement group was 6.2.

Example 2

A 26 year old male was admitted to the Intensive Therapy Unit following a road traffic accident, with generalised cerebral swelling and a closed fracture

of his right tibia and fibula (Tscherne C3). Intra-compartmental monitoring within the right tibialis anterior began 11 hours post injury prior to transfer to theatre for IM nailing. Clinically, the leg appeared very swollen and tight, but no subjective data was available as he was ventilated and sedated for his head injury. Following intramedullary nailing of the tibial fracture, concern was raised as to the presence of ACS, and ICP monitoring had revealed a delta pressure (diastolic blood pressure - ICP) of 30 or less prior to, and throughout his surgery (current guideline for diagnosis of ACS). Full four compartment fasciotomies were performed and bulging, boggy muscle was revealed, with some dark areas of muscle suggesting ischaemia. On return to theatre 48 hours later, the muscle appeared healthy, several small open biopsies were taken, and the wounds were closed with split skin grafts. Clinically he had no residual signs or symptoms attributable to ACS at his 8 week follow up appointment.

The pH and absolute pressure readings during theatre have been plotted on the graph shown in Fig 5, while fig 7 shows pH results compared with the delta pressure recordings.

It is clear that the muscle pH reduced significantly during sustained high ICP, and recovered following fasciotomies.

Example 3

A 19 year old male sustained an open fracture of the left tibial shaft (Gustilo I) when he was knocked off his pedal bike. Monitoring commenced in theatre following anaesthesia and wound debridement, to maintain sterility. The results can be seen in figs 6 and 8.

The muscle pH remained in the physiological range throughout the operation, while neither the absolute ICP, nor the delta pressure met the current criteria for diagnosing ACS. At no point did the patient show any signs of impending or missed ACS.

Modifications and improvements can be made without departing from the scope of the invention.

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1 **Matsen FA.** Compartment syndrome: A unified approach. *Clinical Orthopaedics* 1975; 113: 8.

2 **Robinson CM, O'Donnell J, Will E, Keating JF.** Dropped hallux after the intramedullary nailing of tibial fractures. *Journal of Bone and Joint Surgery (Br)* 1999; 81-B: 481-4.

3 **Mars M, Hadley GP.** Raised intracompartmental pressure and compartment syndromes. *Injury 1998; 29;* 403-411.

4 **Whitesides TE, Haney TC, Morimoto K, Harada H.** Tissue pressure measurements as a determinant for the need for fasciotomy. *Clinical Orthopaedics* 1975; 113: 43.

5 **Heppenstall RB, Sapega AA, Scott R et al .** The compartment syndrome. *Clinical Orthopaedics* 1988; 226: 138-155.

6 **Willy C, Gerngross H, Sterk J.** Measurement of Intracompartmental pressure with the use of a New Electronic Transducer-tipped Catheter System. *Journal of Bone and Joint Surgery (Am)* 1999, 81-A: 158-168.

fig1

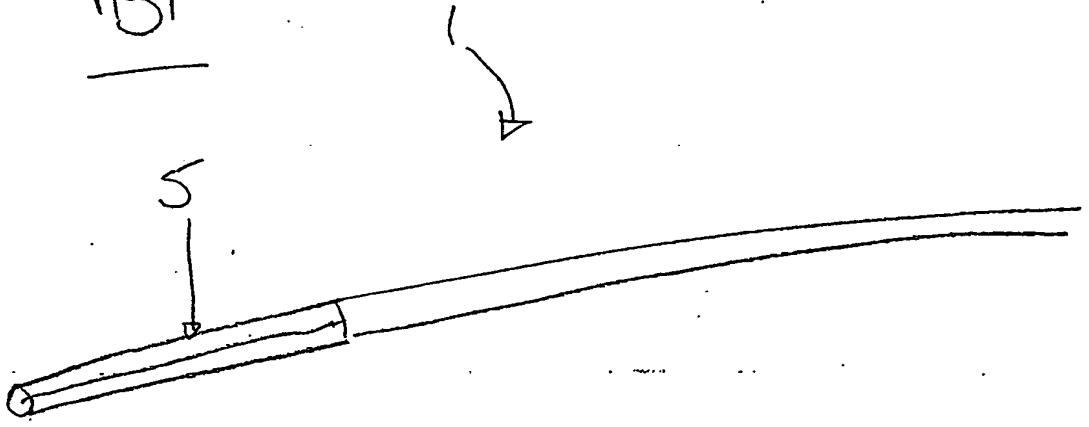


fig2

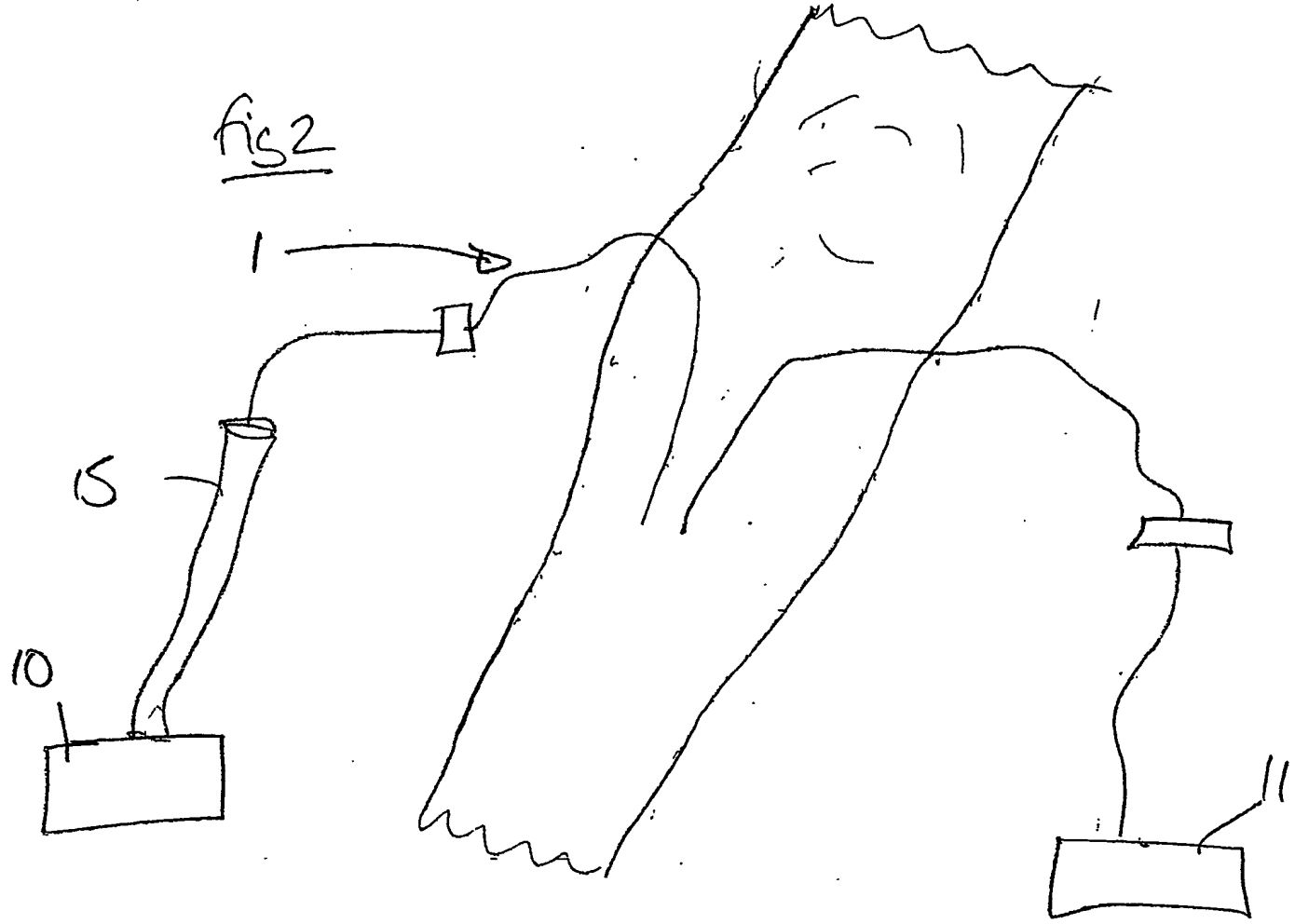


fig3b

Mean intramuscular pH change during tourniquet ischaemia in total knee replacement (n=12)

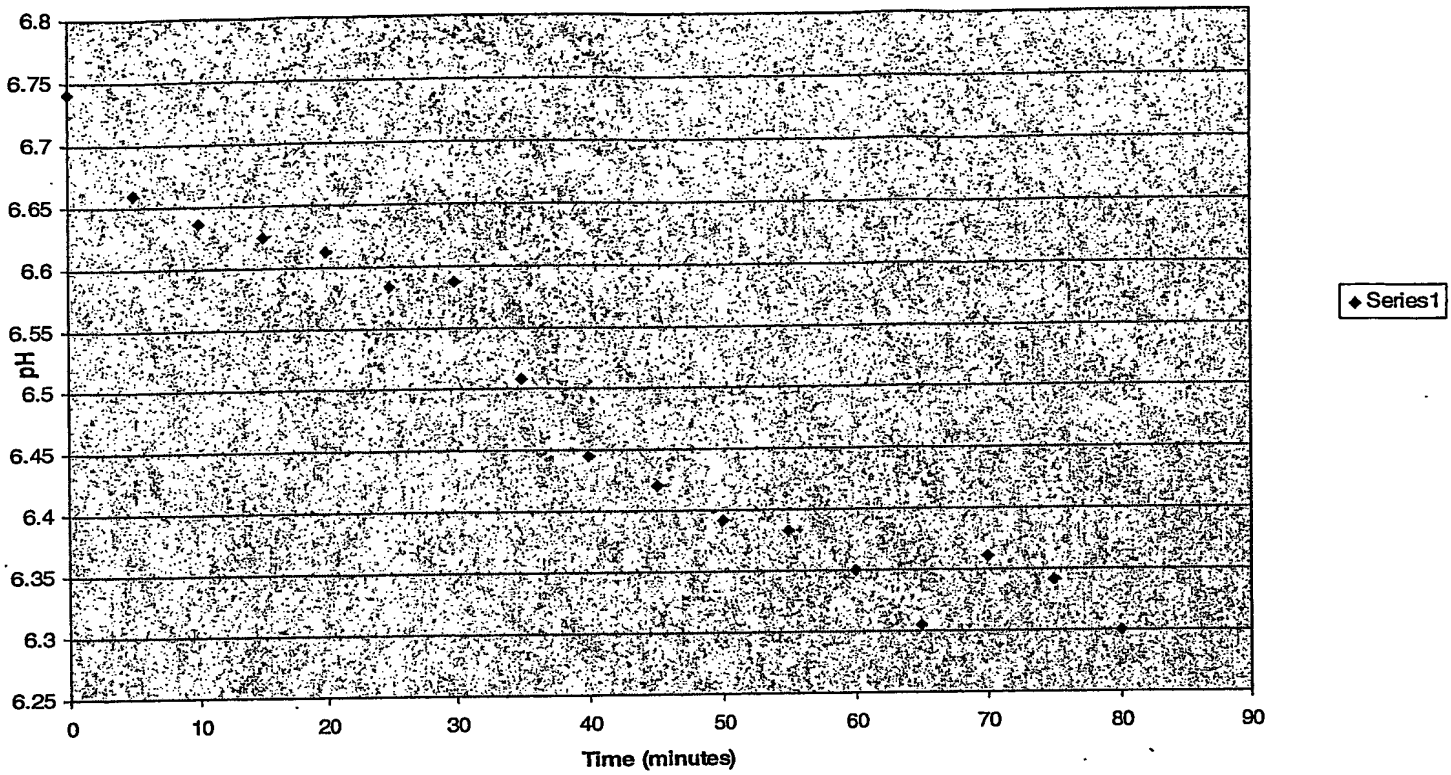


fig4b

Mean intramuscular pH change during re-perfusion following total knee replacement (n=12)

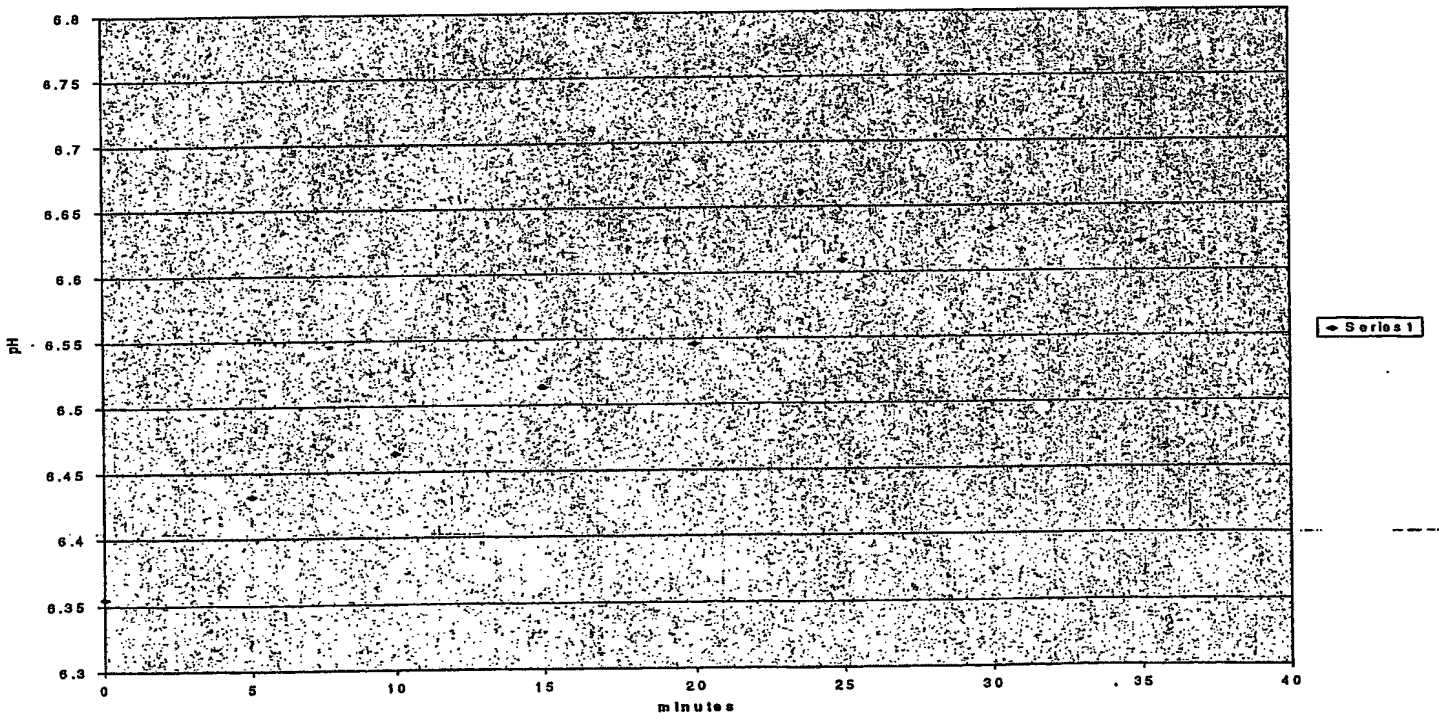


Fig 3a

Graph 1: pH during tourniquet inflation in TKR

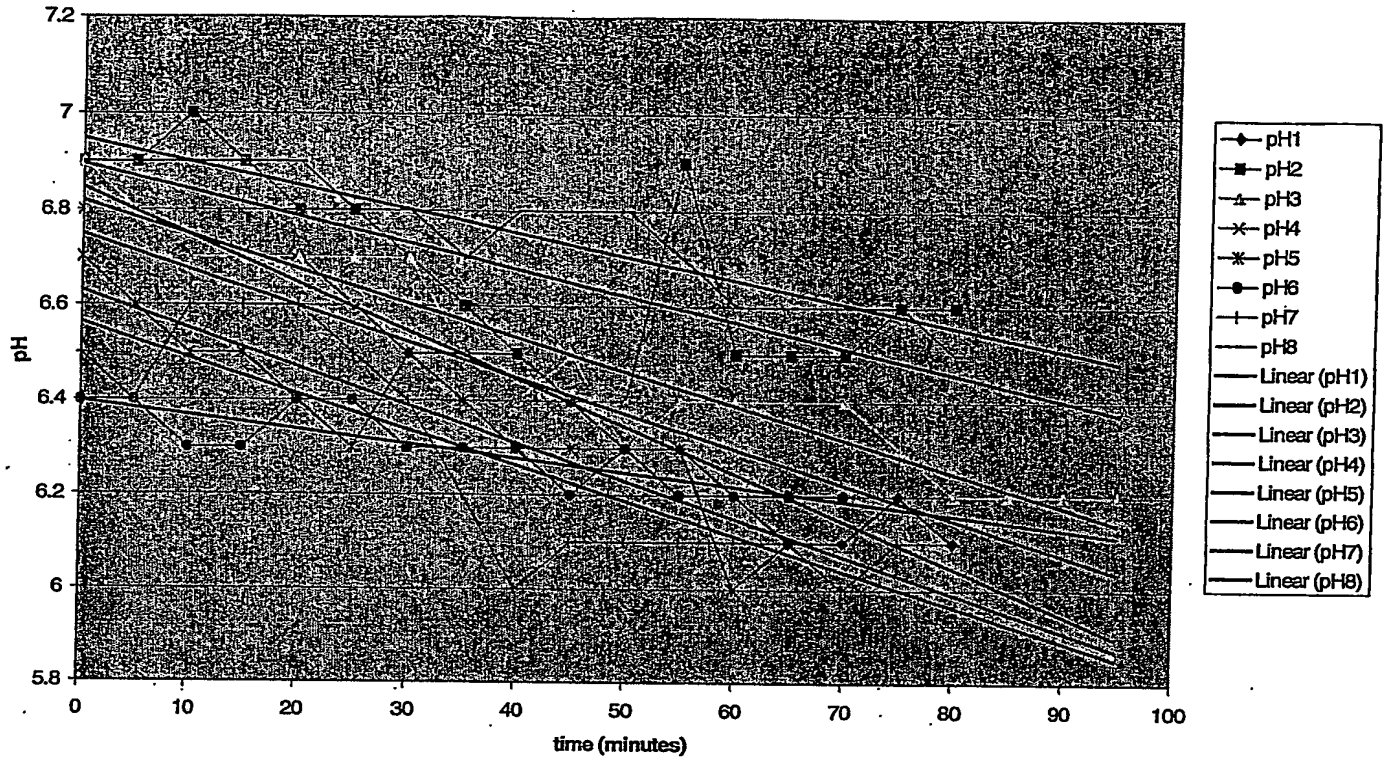


Fig 4a

Graph 2: pH following release of tourniquet in TKR

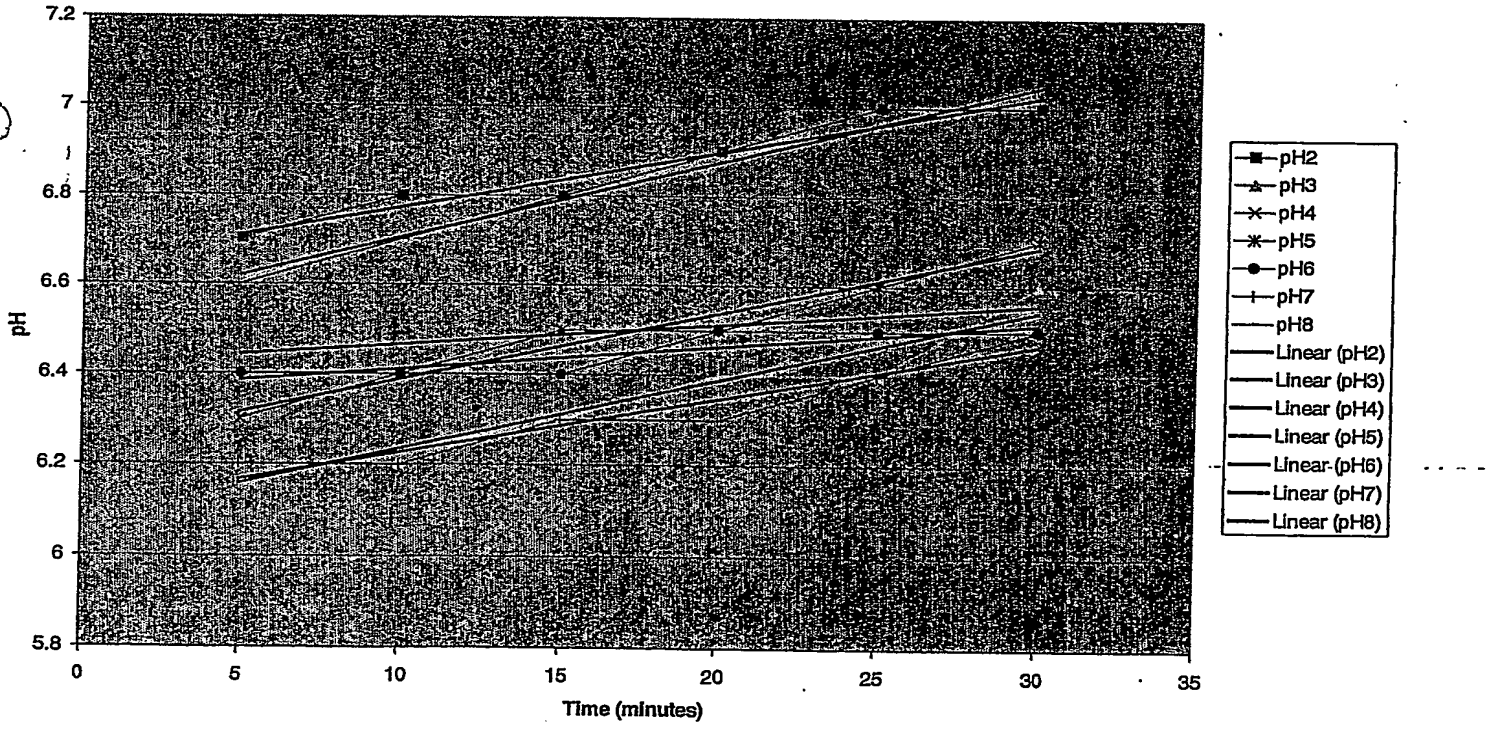


Fig 5

Graph 3: pH vs. absolute ICP during IM nailing
Case 1: ACS

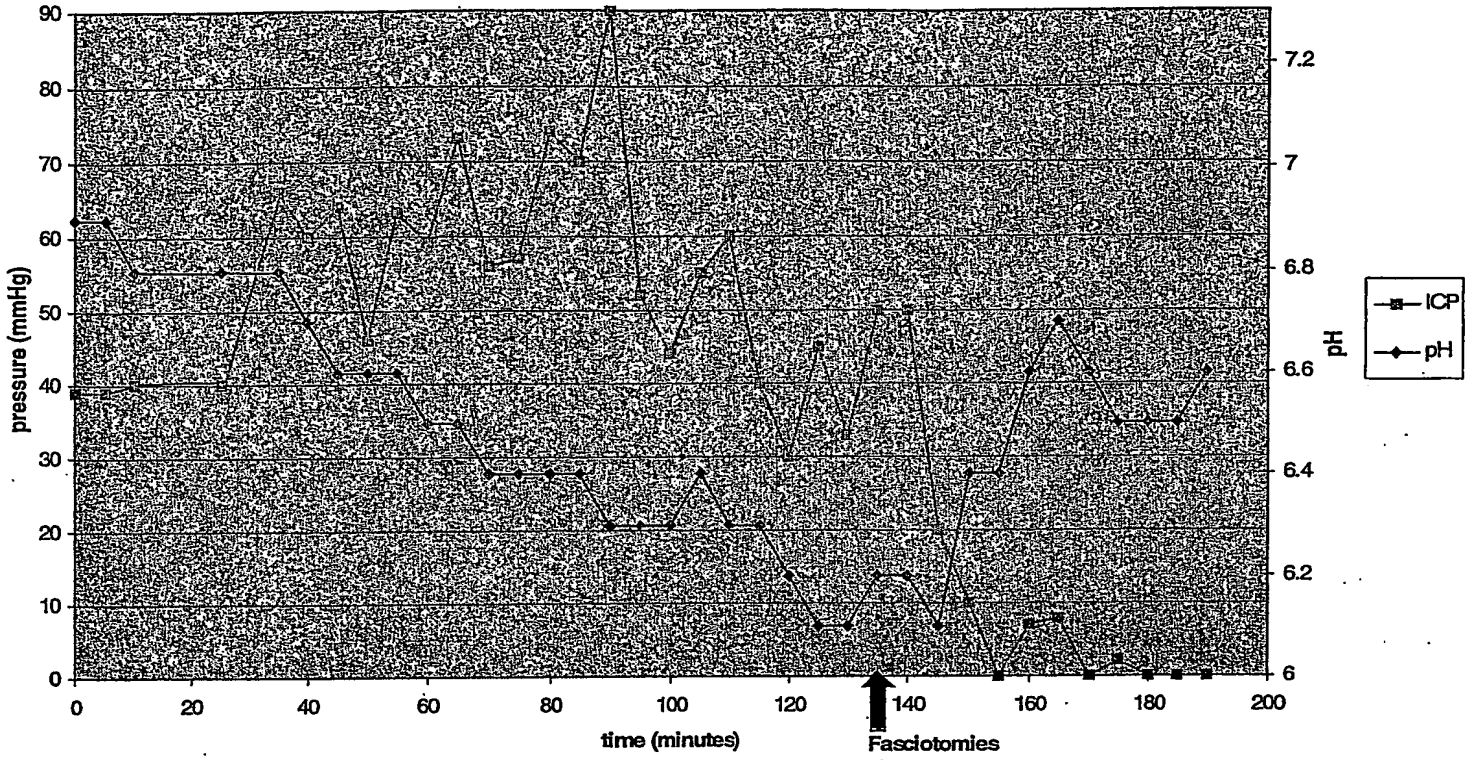


Fig6

Graph 4: pH vs. absolute ICP during IM nailing
Case 2: No ACS

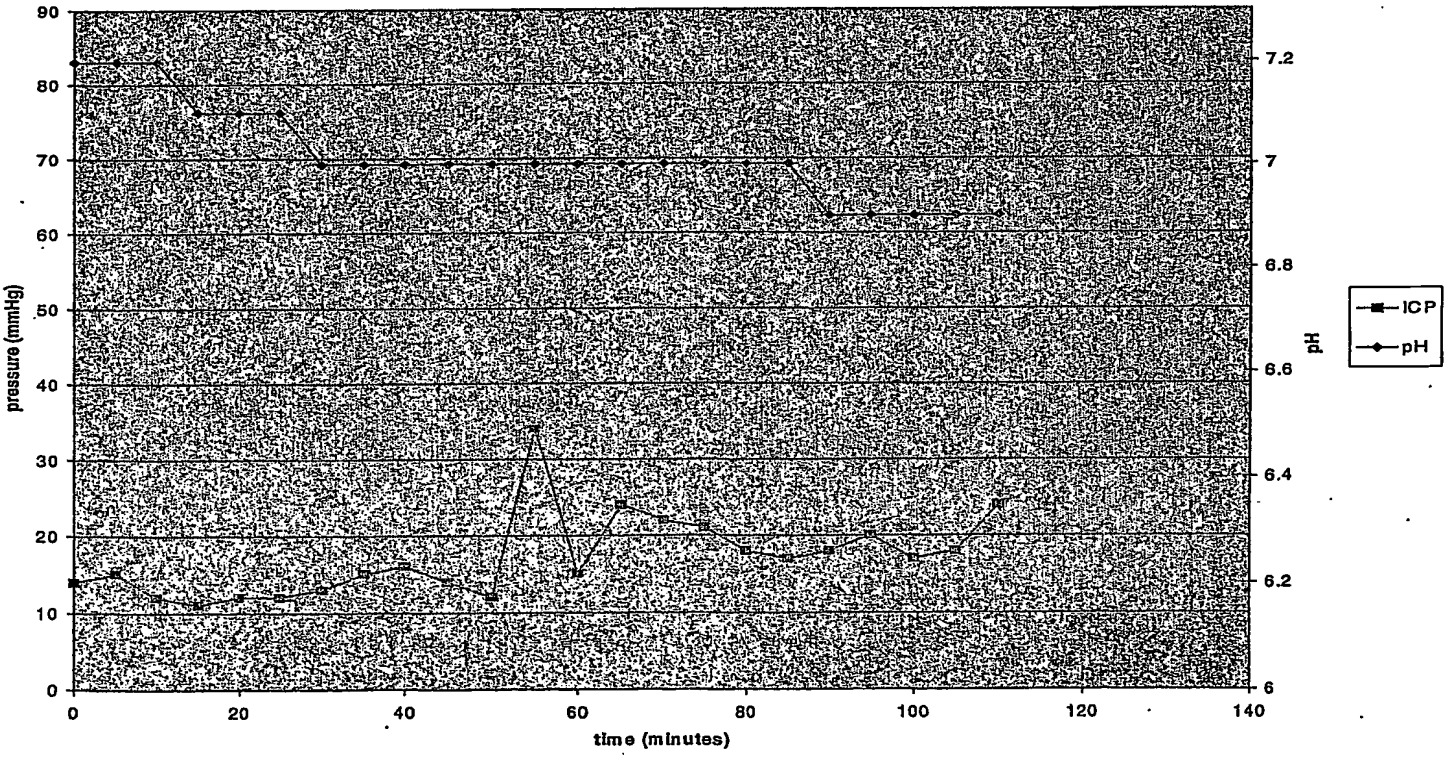


Fig 7

Graph 5: pH vs. delta pressure (DBP-ICP)
Case 1: ACS

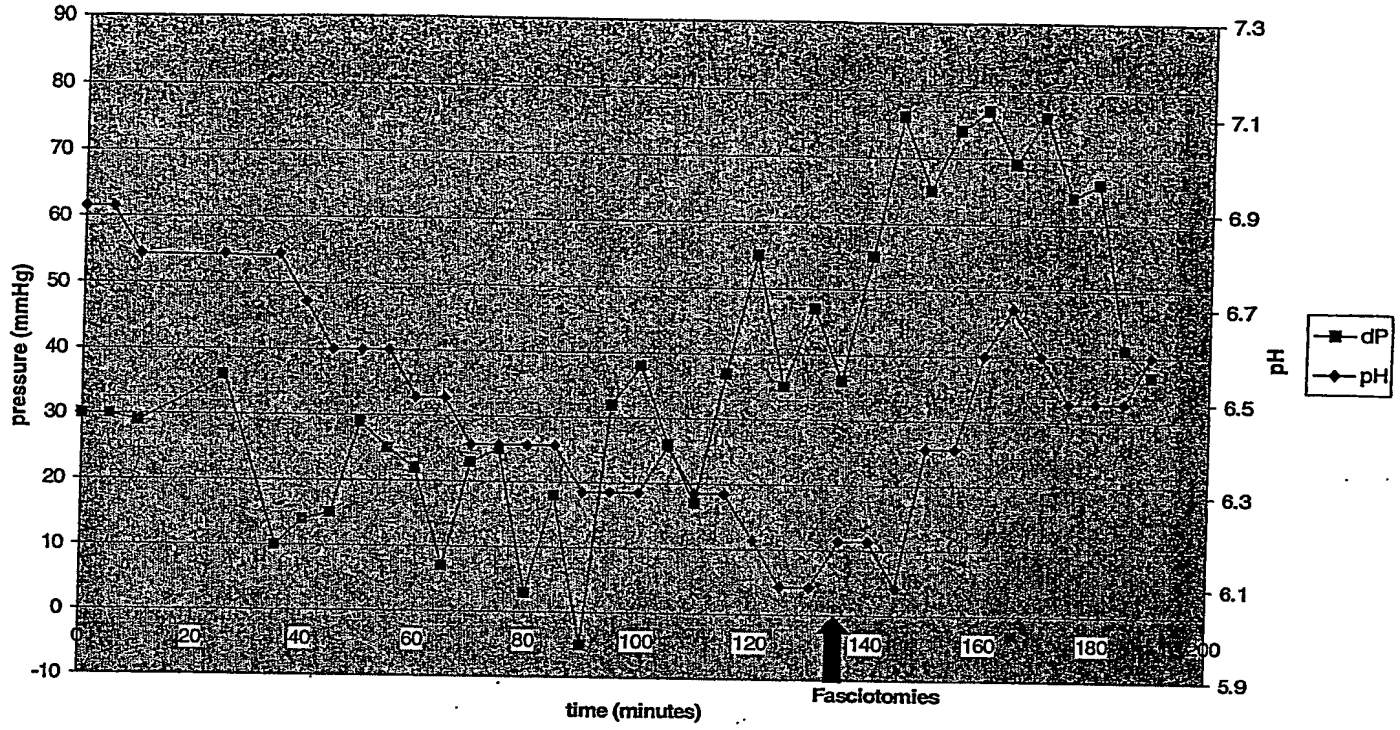
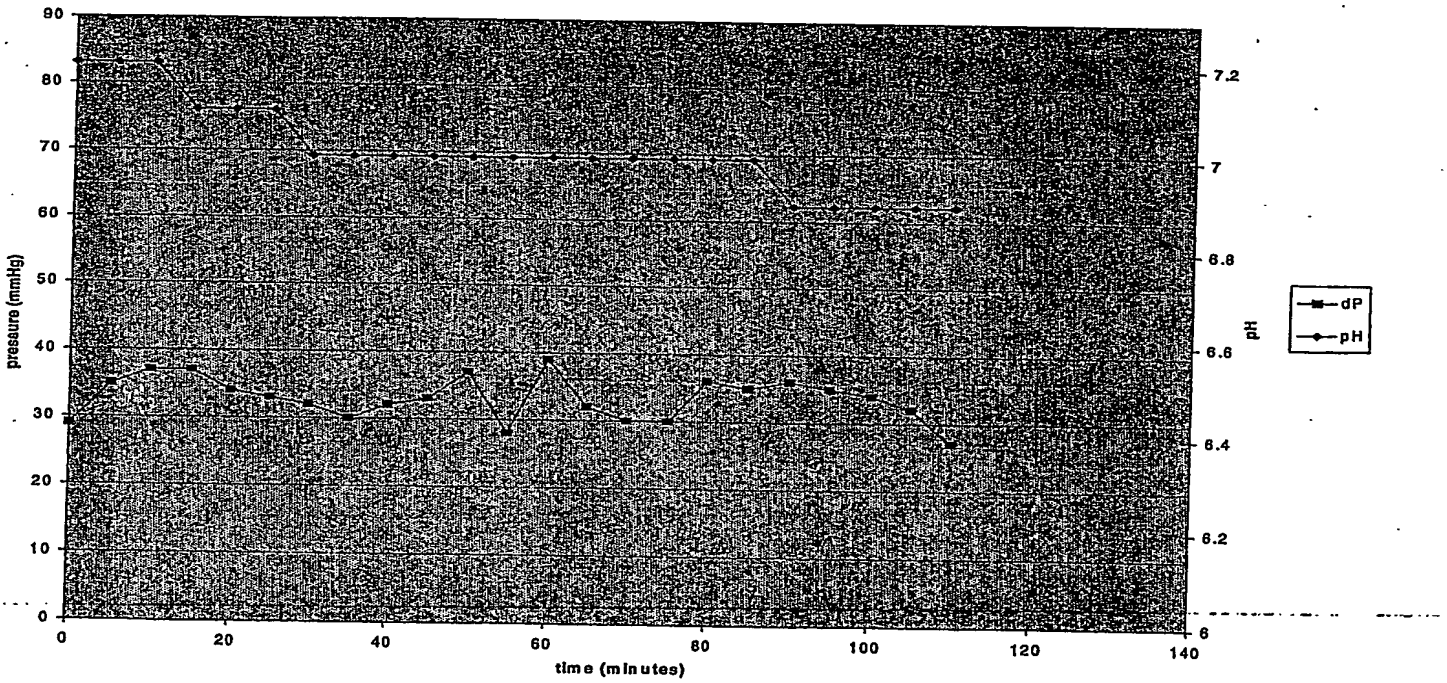


Fig 8

Graph 6: pH vs. delta pressure (DBP-ICP) during IM nailing
Case 2: No ACS



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